OIPE JC102
JAN 29 2003
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Peter S. Linsley et al.
Serial No.:	09/609,915
Filed:	July 3, 2000
Docket:	30436.30USI2
Title:	SOLUBLE CTLA4 MUTANT MOLECULES AND USES THEREOF

CERTIFICATE UNDER 37 CFR 1.8
I hereby certify that this paper or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on January 14, 2003.

By: _____
Name: Tracy Truick

Assistant Commissioner for Patents
Washington, D.C. 20231

Madam:

We are transmitting herewith the attached:

☒ Transmittal sheet, in duplicate, containing Certificate under 37 CFR 1.8.
☒ Supplemental Information Disclosure Statement (37 C.F.R. §1.97 (b)(3))
☒ Form 1449 (Information Disclosure Statement)
☒ Exhibits 115 -216
☒ Return postcard

Please charge any additional fees or credit overpayment to Deposit Account No. 50-0306. A duplicate of this sheet is enclosed.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Peter S. Linsley et al.	**Examiner:**	Elaine-M. Lazar Wesley
Serial No.:	09/609,915	**Group Art Unit:**	1646
Filed:	July 3, 2000	**Docket No.:**	30436.30USI2
Title:	SOLUBLE CTLA4 MUTANT MOLECULES AND USES THEREOF		

CERTIFICATE UNDER 37 CFR 1.8:
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on January 14, 2003.

By: Tracy Truick

55 South Lake Avenue
Suite 710
Pasadena, California 91101
January 14, 2003

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b) 3))

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This Information Disclosure Statement is being filed herewith as a supplement to Applicant's April 2, 2001, Information Disclosure Statement which was submitted under 37 C.F.R.§1.97 (b)(3) before the mailing date of the first Office Action on the merits. In accordance with 37 C.F.R. §1.98(d), copies of Exhibits 115-216 as set forth in the Form 1449 are included herewith.

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner. They are as follows:

- Linsley, et al., 1991, *J.Exp.Med.*"CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7" 174:561-569. **(Exhibit 115)**

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- Gimmi, et al., 1993, *Proc.Natl.Acad.Sci. USA* "Human T-Cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation" 90:6586-6590. **(Exhibit 116)**
- Azuma et al., 1993 *Nature* "B70 antigen is a second ligand for CTLA-4 and CD28" 366:76-79. **(Exhibit 117)**
- Ronchese et al., 1994 *J.Exp.Med* "Mice Transgenic for a Soluble Form of Murine CTLA-4Show Enhanced Expansion of Antigen-specific CD4 T Cells and Defective Antibody production In Vivo" 179:809-817. **(Exhibit 118)**
- Griggs et al., 1996 *J.Exp.Med* "The Relative Contribution of the CD28 and gp39 Costimulatory pathways in the Clonal Expansion and Pathgenic Acquistion of Self-reactive T Cells" 183:801-810. **(Exhibit 119)**
- Verwilghen et al., 1994 *J-Immunol.* Expressionof Functional B& and CTLA4 on Rheumatoid Synovial T Cells" 153:1378-1385. **(Exhibit 120)**
- Blazar et al., 1994 *Blood* "In Vivo Blockade of CD28/CTLA4: Interaction With CTLA4-Ig Reduces Lethal Murine Graft-Versus-Host Disease Across the Major Histocompatiblity Complex Barrier in Mice" 83:3815-3825. **(Exhibit 121)**
- Finck et al., *Science* "Treatment of Murine lupus with CTLA4Ig" 265:1225-1227. **(Exhibit 122)**
- Perrin et al., 1995 *J-Immunol* "Role of B7:CD28/CTLA4 in the Induction of Chronic Relapsing Experimental Allergic Encephalomyelitis" 154:1481-1490. **(Exhibit 123)**
- Pearson et al., 1994 *Transplantation* "Transplantation Tolerance Induced By CTLA4-Ig" 57:1701-1706. **(Exhibit 124)**
- Baliga et al., 1994 *Transplantation* "CTLA4Ig PROLONGS ALLOGRAFT SURVIVAL WHILE SUPPRESSING CELL-MEDIATED IMMUNITY" 58:1082-1090. **(Exhibit 125)**
- Tepper et al., 1994 *Transplantation Proceedings* "Tolerance Induction by soluble CTLA4 in a Mouse Skin Transplant Model" 26:3151-3154. **(Exhibit 126)**

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- Perico et al., 1995 *Kidney International* "Toward novel antirejection strategies: In *vivo* immunosuppressive properties of CTLA4Ig" 47:241-246. **(Exhibit 127)**
- Finck et al., 1994 *Arthritis and Rheumatism* "Effects of CTLA4Ig in murine lupus" 37:S222. **(Exhibit 128)**
- Nishikawa et al., 1994 *Eur J. Immunol.* "Effect of CTLA-4 chimeric protein on rat autoimmune anti-glomerular basement membrane glomerulonephritis" 24:1249-1254. **(Exhibit 129)**
- Wallace et al., 1994 *Transplantation* "CTLA4ig treatment ameliorates the lethality of murine graft-versus-host disease across major histocompatibility complex barriers" 58:602-610. **(Exhibit 130)**
- Damle et al., *J. Immunol.* "Costimulation of T Lymphocytes with integrin Ligands intercellular Adhesion Molecule-1 or Vascular Cell Adhesion Molecule-1 Induces Functional Expression of CTLA-4, a Second Receptor for B7" 152:2686-2697. **(Exhibit 131)**
- Milich, et al., 1994 *J. Immunol* "Soluble CTLA-4 can suppress autoantibody production and elicit long term unresponsiveness in a novel transgenic model," 153:429-435. **(Exhibit 132)**
- Webb, et al., 1996 *Eur J. Immunol* "Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2," 26:2320-2328. **(Exhibit 133)**
- Van Oosterhout, et al., 1997 *Am.J.Respir.Cell Mol.Biol* ."Murine CTLA4-IgG Treatment Inhibits Airway Eosinophilia and Hyperresponsiveness and Attenuates IgE Upregulation in a Murine Model of allergic Asthma," 17:386-392. **(Exhibit 134)**
- Abrams et al., 1999 *J-Clin-Invest* "CTLA4Ig-mediated blockade of T-cell costimuation in patients with psoriasis vulgaris. 103:1243-1252. **(Exhibit 135)**
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- Lenschow, et al., 1995 *J Exp Med* "Differential Effects of anti-B7-1 and Anti-b&-2 Monoclonal Antibody Treatment on the Development of Diabetes in the Nonobese Diabetic Mouse," 181:1145-1155. **(Exhibit 137)**
- Lenschow, et al., 1992 *Science* "Long-Term Survival of Xenogeneic Pancreatic islet Grafts Induced by CTLA4Ig," 257:789-792. **(Exhibit 138)**
- Sayegh., 1999 *J Clin Invest* "Finally, CTLA4Ig graduates to the clinic," 103:1223-1225. **(Exhibit 139)**
- Wolfe, 1995 *Bailliere's Clinical Rheumatology* "The epidemiology of drug treatment failure in rheumatoid arthritis," 9:619-632. **(Exhibit 140)**
- Hochberg, et al., 1990 *Epidemiologic Reviews* "Epidemiology of Rheumatoid Arthritis: Update," 12:247-252. **(Exhibit 141)**
- Spector, 1990 *Epidemiology of Rheumatic Disease* "Rheumatoid Arthritis," 16:513-537. **(Exhibit 142)**
- Liu MF, Kohsaka H Sakurai H, Azuma m Okumura K Saito I, Miyasaka N, 1996. "The presence of costimulatory molecules B7.1 (CD80) and B7.2 (CD86) in rheumatoid arthritis synovium" *Arthritis-Rheum.* Jan; 39(1): 110-4. **(Exhibit 143)**
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- Sayegh MH, Akalin E, Hancock WW, Russell ME, Carpenter CB, Linsley PS, Turka LA, 1995. *J. Exp. Med.*"CD28-B7 blockade after allantigenic challenge in vivo inhibits Th1 cytokines but spares Th2". 181: 1869-1874. **(Exhibit 145)**
- Racusen LC; et. al. 1999. "The Baniff 97 working classification of renal allograft pathology". *Kidney-Int.* 55(2): 713- 723. **(Exhibit 146)**
- Parkin D, Jacoby A, McNamme P, 2000. "Treatment of multiple sclerosis with interferon β: an appraisal of cost-effectiveness and quality of life" *J Neurol Neurosurg Psychiatry*; 68: 144-149. **(Exhibit 147**

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- Pearson TC, Alexander DZ, Winn KJ, Linsley PS, Lowry RP, Larsen CP, 1994. "Transplantation tolerance induced by CTLA4-Ig. *Transplantation*, 57:1701-1706. **(Exhibit 149)**
- Liao HX, Haynes BF, 1995. "Role of adhesion molecules in the pathogensis of rheumatoid arthritis" *Rheum-Dis-Clin-Noth-Am.* Aug; 21(3): 715-40. **(Exhibit 150)**
- PCT No. WO 95/33770, December 14, 1995. **(Exhibit 151)**
- Thomas R, Quinn C. 1996. "Functional differentiation of dendritic cells in rheumatoid arthritis: role of CD86 in the synovium" *J-Immunol.* Apr 15; 156(8): 3074-86. **(Exhibit 152)**
- Verhoeven-AC; Boers-M; Tugwell-P, 1998. "Combination therapy in rheumatoid arthritis: updated systematic review" *Br-J-Rheumatol.* Jun;37 (6): 612-619 **(Exhibit 153)**
- Schiff M, 1997. "Emerging treatments for rheumatoid arthritis" *Am-J-Med.* Jan 27; 102 (1A): 11S-15S **(Exhibit 154)**
- Balsa A, Dixey J, Sansom DM, Maddison PJ, Hall ND, 1996. "Differential expression of the costimulatory molecules B7.1 (CD80) and B7.2 (CD86) in rheumatoid synovial tissue" *Br-J-Rheumatol.* Jan; 35(1): 33-7 **(Exhibit 155)**
- Ranheim Ea, Kipps Tj, 1994. "Elevated expression of CD80 (B7/BB1) and other accessory molecules on synovial fluid mononuclear cell subsets in rheumatoid arthritis" *Arthritis-Rheum.* Nov;37 (11): 1637-1647 **(Exhibit 156)**
- Freeman, GJ, Gribben JG, Boussiotis VA, et. al. 1993. "Cloning of B7-2: a CTLA-4 counter receptor that costimulates human T cell proliferation" *Science*, 262: 909-911. **(Exhibit 157)**
- Becker, J.C., March 8, 2001, Abstract and of Presentation of "A multi-center, randomized, double-blind, placebo controlled study to evaluate the safety and

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- Aruffo, S., March 27, 2000, Presentation of "Approaches to Immune Regulation" at BIO 2000 in Boston, Mass. **(Exhibit 159)**
- Abrams, et al., September 4, 2000, *J.Exp.Med.* "Blockade of T Lymphocyte Costimulation with Cytotoxic T Lymphocyte- associated Antigen 4-Immunogloblin (CTLA4Ig) Reverse the Cellular Pathology of Psoriatic plaques, Including the Activation of Keratinocytes, Dendritic Cells, and Endothelial Cells, " 192:681-693. **(Exhibit 160)**
- Srinivas, N.R. et al., December 1, 1995, *J.Pharmaceutical Sciences* "Pharmacokinetics and pharmacodynamics of CTLA4Ig (BMA-188667), a Novel Immunosuppressive Agent, in Monkeys following Multiple Doses," 85:1-4. **(Exhibit 161)**
- Gandhi, et al., November 18, 1998, Abstract and Presentation of *PharmSci Supplement* "Physical and Chemical Characterization of BMS-224818, A Recombinant Fusion Protein," in San Francisco, Ca. **(Exhibit 162)**
- Flesher, A.R., April 15, 1999, *Biological Process Sciences* Presentation of 'Transgenic Production, A Comparative Study" at Bio 99 in Seattle, Washington. **(Exhibit 163)**
- Greve, K.F., May 9, 1996, *J Chromatography* "Capillary electrophoretic examination of underivatized oligosaccharide mixtures released from immunoglobulin G anitbodies and CTLA4Ig fusion protein," 749:237-245. **(Exhibit 164)**
- Srinivas, N.R., April 8, 1997, *Pharmaceutical Research* "Assessment of Dose Proportionality, Absolute Bioavailability, and Immunogenicity Response of CTLAIg (BMS-188667), a Novel Immunosuppressive Agent, Following Subcutaneous and Intravenous Administration to Rats," 14:911-916. **(Exhibit 165)**
- Weiner, R.S., November 6-10, 1994, Abstract and Presentation of "Validation and PK Application of a Double Antibody Sandwich Enzyme Immunoassay For the

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- Weiner, R.S., June 6, 1996, *J Pharmaceutical and Biomedical Analysis* "A sensitive enzyme immunoassay for the quantitation of human CTLA4Ig fusion protien in mouse serum: pharmacokinetic application to optimizing cell line selection," 15:571-579. **(Exhibit 167)**
- Warner, G.I. et al., March 16-22, 1995, Abstract and Presentation of "Bioactivity of BMS-188667 (CTLAIg) in Cynomolgus Monkeys," in Seattle, Washington. **(Exhibit 168)**
- Weiner, R.S., March 1, 2000, Abstract and Presentation of "Industrial Perspectives of Primary Analytical Tools for Macromaloecules- Principles and Applications with Examples." **(Exhibit 169)**
- Weiner, R.S., November 1995 Abstract and Presentation of "Validation of an Enzyme Immunoassay For The Quantition of Human CTLAIg Fusion Protein In Human Serum," in Miami, Florida. **(Exhibit 170)**
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- Webb, L.M.C. et al., July 23, 1996 *Eur J Immunol* "Prevention and amelioration of collagen-induced arthritis by blocade of the CE28 co-stimulatory pathway: requirement for both B7-1 and B7-2" 26:2320-2328. **(Exhibit 172)**
- Knoerzer, et al., May 5, 1995, *J Clin. Invest* "Collagen-induced Arthritis in the BB Rat Prevention of Disease by Treatment with CTLA4Ig" 96:987-993. **(Exhibit 173)**
- Larsen, et al., April 27, 2000, Abstract of "Prolongation of Renal Allograft Survival with Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-IG Fusion Protein In Non-Human Primates," in *Transplantation,* 69(8): #44, p. S123, Chicago, Il. **(Exhibit 174)**

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- Larsen, et al., May 13-17, 2000, A Presentation of "Prolongation of Renal Allograft Survival With Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-Ig Protein In Nonhuman Primates" at the American Society of Transplantation Meeting in Chicago, Il. **(Exhibit 175)**
- Larsen, Aug. 27-Sept.1, 2000, A Presentation of "Manipulation of Costimulatory Pathways: Targeting CD80 and CD86" at the XVII congress of the Transplantation Society in Rome, Italy. **(Exhibit 176)**
- Larsen, March 3-4, 2000, A Presentation of "Costimulation blockade: progress toward clinical application" at Canadian Society of Transplantation Annual Scientific meeting in Mont Tremblant, Quebec, Canada. **(Exhibit 177)**
- Larsen, Jan. 13-17, 2000, A Presentation of "Costimulation blockade: Progress toward clinical application" at the American Society of Transplantation Meeting in Las Croabas, Puerto Rico. **(Exhibit 178)**
- Hathcock, et al., August 30, 1993 *Science* "Identification of an Alternative CTLA-4 Ligand Costimulatory for t Cell Activation," 262:905-911. **(Exhibit 179)**
- Sfikakis, et al., November 29, 1994 *Arthritis & Rheumatism* "CD28 Expression On T Cell Subsets in Vivo And CD28-Mediated T Cell Response In Vitro In Patients With Rheumatoid Arthritis," 38:649-654. **(Exhibit 180)**
- U.S. Patent No. 5,434,131, July 18, 1995. **(Exhibit 181)**
- PCT No. WO 02/02638 A2, January 10, 2002. **(Exhibit 182)**
- Lakkis, Fadi G., et al., "Blocking the CD28-B7 T Cell Costimulation Pathway Induces Long Term Cardiac Allograft Acceptance in the Absence of IL-4[1]," *The Journal of Immunology,* 1997, 158:2443-2448. **(Exhibit 183)**
- Pearson, Thomas C., et al., "ANALYSIS OF THE B7 COSTIMULATORY PATHWAY IN ALLOGRAFT REJECTION[1]," *Transplantation,* 1997, 63:1463-1469. **(Exhibit 184)**
- Pearson, Thomas C., et al., "TRANSPLANTATION TOLERANCE INDUCED BY CTLA4-Ig[1]," *Transplantation,* 1994, 57:1701-1706. **(Exhibit 185)**

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- Alexander, Diane Z., "ANALYSIS OF A FUNCTIONAL ROLE FOR CHIMERISM IN CTLA4-Ig PLUS BONE MARROW-TREATED CARDIAC ALLOGRAFT RECIPIENTS," *Transplantation,* 1994, 91:416-418. **(Exhibit 186)**
- Larsen, Christian P., et al., "CD40-gp39 INTERACTIONS PLAY A CRITICAL ROLE DURING ALLOFRAFT REJECTION" *Transplantation,* 1996, 61:4-9. **(Exhibit 187)**
- Pearson, Thomas C., et al., "CTLA4-Ig PLUS BONE MARROW INDUCES LONG-TERM ALLOGRAFT SURVIVAL AND DONOR-SPECIFIC UNRESONSIVENESS IN THE MURINE MODEL", *Transplantation,* 1996, 61:997-1004. **(Exhibit 188)**
- Weber, C.J., et al., "CTLA4-Ig Prolongs Survival of Microencapsulated Rabbit Islet Xenografts in Spontaneously Diabetic Nod Mice," *Transplantation Proceedings,* 1996, 28:821-823. **(Exhibit 189)**
- Alexander, D.Z., et al., "Analysis of effector mechanisms in murine cardiac allograft rejection," *Transplantation Immunology,* 1996 , 4:46-48. **(Exhibit 190)**
- Larsen, Christian P., et al., "Long-Term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways," *Nature,* 1996, 381:434-438. **(Exhibit 191)**
- Elwood, Eric T., et al., "Microchimerism and rejection in clinical transplantation," *The Lancet,* 1997, 349:1358-1360. **(Exhibit 192)**
- Larsen, Christian P., and Thomas C. Pearson., "The CD40 pathway in allograft rejection, acceptance, and tolerance," *Transplantation,* 1997,9:641-647. **(Exhibit 193)**
- Konieczny, Bogumila T.., et al., "IFN-γ Critical for Long-Term Allograft Survival Induced by Blocking the CD28 and CD40 Ligand T Cell Constimulation Pathways[1]," *The Journal of Immunology,* 1998,160:2059-2064. **(Exhibit 194)**
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- Niimi, Masanori, et al., "The Role of the CD40 Pathway in Alloantigen-Induced Hyporesonsiveness in Vivo1," The Journal of Immunology, 1998,161:5331-5337. **(Exhibit 196)**

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- Bingaman, Adam W., et al., "Vigorous Allograft Rejection in the Absence of Danger1," Journal of Immunology, 2000,164:3065-3071. **(Exhibit 198)**
- Bingaman, Adam W., et al., "TRANSPLANTATION OF THE BONE MARROW MICROENVIROMENT LEADS TO HEMATOPPIETIC CHIMERISM WITHOUT CYTOREDUCTIVE CONDITIONING," Transplantation, 2000, 69:2491-2496. **(Exhibit 199)**
- Durham, Megan M., et al., "Cutting Edge: Administration of Anti-CD40 Ligand and Donor Bone Marrow Leads to Hemapoietic Chimerism and Donor-Specific Tolerance Without Cytoreductive Conditioning[1]," *Cutting Edge,* 2000,165:1-4. **(Exhibit 200)**
- Williams, Matthew A., et al., "Genetic Characterization of Strain Differences in the Ability to Mediate CD40/CD28-Independent Rejection of Skin Allografts[1]," *The Journal of Immunology,* 2000, 165: 6549-6857. **(Exhibit 201)**
- Bingaman, Adam W., et al., "The role of CD40L in T cell-dependent nitric oxide production by murine macrophages," *Transplant Immunology,* 2000, 8:195-202. **(Exhibit 202)**
- Adams, Andrew B., et al., "Costimulation Blockade, Busulfan, and Bone Marrow Promote Titratable Macrochimerism, Induce Transplantation Tolerance, and Correct Genetic Hemoglobinopathies with Minimal Myelosuppression[1]," *The Journal of Immunology,* 2001, 167:1103-1111. **(Exhibit 203)**
- Meng, L., "Blockade of the CD40 Pathway Fails to Prevent CD8 T Cell-Mediated Intestinal Allograft Rejection," *Transplantation Proceedings,* 2001, 33:418-420. **(Exhibit 204)**
- Guo, Zhong., et al., "CD8 T CELL-MEDIATED REJECTION OF INTESTINAL ALLOGRAFTS IS RESISTANT TO INHIBITION OF THE CD40/CD154

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COSTIMULATORY PATHWAY," *Transplantation,* 2001, 71:1351-1354. **(Exhibit 205)**

- Ha, Jongwon., et al., "Aggressive skin allograft rejection in CD28$^{-/-}$ mice independent of the CD40/CD40L costimulatory pathway," *Transplant Immunology,*2001, 9:13-17. **(Exhibit 206)**
- Bingaman, Adam W., et al., "ANALYSIS OF THE CD40 AND CD28 PATHWAYS ON ALLOIMMUNE RESPONSES BY CD4$^+$ T CELLS IN VIVO[1]," *Transplantation,* 2001, 72:1286-1292. **(Exhibit 207)**
- Adams, Andrew B., et al., "Calcineurin Inhibitor- Free CD28 Blockade-Based Protocol Protects Allogeneic Islets in Nonhuman Primates," *Diabetes,* 2002, 51:265-270. **(Exhibit 208)**
- Whelchel, JD., et al. "Evolving Strategies in immunosuppressive Therapy: The Emory Experience," *Clinical Transplants*, 1996, 20:249-255 **(Exhibit 209)**
- Ritichie, SC., et al., "Regulation of Immunostimulatory function and B7 molecule expression on murine dendritic cells," *Journal of Cellular Biochemistry,*1995,21A:C1-215**(Exhibit 210)**
- Alexander, DZ., et al., "Analysis of the mechanisms of CTLA4-Ig plus bone marrow induced transplantation tolerance," *Journal of Cellular Biochemistry*, 1995, 21A:C1-301 **(Exhibit 211)**
- Alexander, DZ., et al., "CTLA4-Ig induced transplantation tolerance: analysis of donor cell chimerism," Surgical Forum, 1994, 45:402-403 **(Exhibit 212)**
- Pearson, TC., et al., "CTLA4-Ig plus bone marrow induces transplantation tolerance in the murine model," Journal of Cellular Biochemistry, 1995, 21A:C1-327 **(Exhibit 213)**
- Lakkis, FG., et al., "CTLA4Ig induces long-term cardiac allograft survival in the absence of interleukin-4," Journal of the American Society of Nephrology, 1996, 7:A3204 **(Exhibit 214)**

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- L104EA29Y (Figure 24, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
- L104EA29Y (Figure 24 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.
  - L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
  - L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
- A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as **Exhibit 215**.
  - The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R.§20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.
  - The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
  - The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 215), which differs from CTLA4Ig at two amino acid residues, Leu_{104}-Glu and Ala_{29}-Tyr (Exhibit 215 at page 2).
- An Investigator Brochure dated January 26, 1999 is enclosed as **Exhibit 216**.
  - The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement,

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more than one year before the priority date of the subject application, i.e. May 26, 2000.

- The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
- The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 216), but not the sequence of L104EA29Y (Figure 24, of the subject application).

No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the references are not "prior art." Applicants wish to reiterate that the documents and information above were not at the time of filing publicly available since they were provided under confidentiality agreements.

Consideration of the items listed is respectfully requested. Applicants invite the Patent Office to request additional information if necessary. Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

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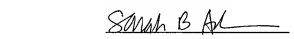
No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-0306.

Respectfully submitted,



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FORM 1449*	Docket Number	Application Number
	30436.30USI2	09/609,915
INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION	Applicant	
	Peter S. Linsley et al.	
	Filing Date	Group Art Unit
(Use several sheets if necessary)	July 3, 2000	1646

OIPE JC02 JAN 29 2003 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	5,434,131 **(Exhibit 181)**	7/18/95	Linsley et al.			5/26/93

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
	WO 95/33770 **(Exhibit 151)**	12/14/95	PCT				X
	WO 02/02638 A2 **(Exhibit 182)**	1/10/02	PCT				X

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		Nishikawa et al., 1994 *Eur J. Immunol.* "Effect of CTLA-4 chimeric protein on rat autoimmune anti-glomerular basement membrane glomerulonephritis" 24:1249-1254. **(Exhibit 129)**
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		Pearson, TC., et al., "CTLA4-Ig plus bone marrow induces transplantation tolerance in the murine model," Journal of Cellular Biochemistry, 1995, 21A:C1-327 **(Exhibit 213)**
		Lakkis, FG., et al., "CTLA4Ig induces long-term cardiac allograft survival in the absence of interleukin-4," Journal of the American Society of Nephrology, 1996, 7:A3204 **(Exhibit 214)**
		L104EA29Y (Figure 24, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
		L104EA29Y (Figure 24 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.

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		L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
		L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
		A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as **Exhibit 215**.
		The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R.§20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.
		The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
		The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 171), which differs from CTLA4Ig at two amino acid residues, Leu104-Glu and Ala29-Tyr (Exhibit 171 at page 2).
		An Investigator Brochure dated January 26, 1999 is enclosed as **Exhibit 216**.
		The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000.
		The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
		The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 172), but not the sequence of L104EA29Y (Figure 24, of the subject application).

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